

design also makes it easier to use a sealer or stopper for the front opening extending out to and beyond the barrel diameter. In the product this property allows the sealer to better center and buffer the external sleeve and in manufacture the same property makes it possible to grip and hold the sealer in an equipment cavity adapted to the barrel diameter, which in turn may be used to eliminate use of the sleeve for sealer manipulation, making sleeve design more free, e.g. in respect of barrel to sleeve distance, and enabling removal of the sleeve from at least the sterile manufacturing zone and enabling independent inspection of the barrel ampoule semi-manufacture.

Use of a barrel with a front opening edge being rounded with the edge material kept within the nominal barrel inner and outer diameters further amplifies these advantages. The property also gives general advantages in bulk or individual handling of the barrels as such, e.g. higher precision and strongly reduced risk for damage and particle release. Sealers and stoppers can more easily and without tumbling risks be attached to the opening with mechanized means, also in the absence of the sleeve as sealer manipulator, and the stoppers as such can be made less elaborate and with less cavity forming parts within the barrel. The invention also provides an ampoule carrier giving substantial general advantages in manufacture of prefilled ampoules. The carrier can be used in most manufacturing steps, reducing bulk treatment and corresponding damage risks for the ampoules. The carrier provides one or more channels for individual ampoules. Channels formed as a cavities in a carrier body and essentially surrounding the ampoule give a protection and contamination confinement similar to the known sleeve. The cavity has been found to assist in a uniform heat conduction and radiation shielding of special importance in lyophilizing processes. If desired the cavity can be made to radially support an ampoule over substantial length and the structure can be made, e.g. by spacers or otherwise, to accommodate ampoules of different lengths or widths, thereby providing a valuable versatility. Although not restricted to any particular

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ampoule form the structure cooperates beneficially with ampoules of the general cylindrical form described. A channel made longer than the ampoule can be used to hold a sealer in a floating, and yet protected, position above but concentric with the ampoule opening for later individually centered and guided axial movement into a closed position, an option of particular value in lyophilization, for allowing first vapor passage past the sealer and later in-situ closure of the powder chamber. When used with a cylindrical barrel type ampoule and slightly oversized sealer as described, these advantages can be obtained with maintained possibilities for ampoule introduction in the channel from the sealer seat side of the carrier, without additional guiding structures. Upper and lower locking surfaces protruding into the channel can be used to restrict ampoule axial movements. A surface separation of at least ampoule height allows the ampoule to reside between the surfaces. A first advantage with this feature is that ampoule ends are used for axial fixation making superfluous any intermediate structures, such as flanges, recesses, bottle neck openings, by-pass structures etc., and accordingly makes the carrier compatible with the most pure ampoule designs described. A further advantage is that all forces applied to the ampoule during manufacture, such as in insertion, filling, piston introduction, sealing and removal, are absorbed in the beneficial axial direction, strongly reducing the risks for ampoule damage and plant contamination. Still, releasable locks may make both channel sides accessible for operational steps, both the direct manufacturing steps but also indirect steps, such as probing and ampoule weighing, providing substantial flexibility in use, especially in combination with turnable carrier arrangements, of value in plants for multiple ampoule types or multiple chamber type ampoules. Movable locking surfaces may be complemented with stop surfaces fixed relative each channel to further reduce the risks for inadvertent compression and excessive forces, of value for example when exact tolerances in size or support cannot be guaranteed.--

Please replace the paragraph starting on page 24, line 21 with the following paragraph:

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--Figure 4 illustrates schematically main steps in a preferred procedural sequence for manufacture of pre-filled dual-chamber syringe type cartridges. Several steps are conducted with a sterile zone, illustrated with dotted line 40. In a first step 41 syringe barrels are washed and siliconized. The so treated barrels are transmitted through a sterile oven 42 at the exit of which they enter the sterile zone 40. In a piston charging step 43 an intermediate piston is inserted into the barrel to delimit the front and the rear chambers. For example, the piston can be inserted through a front end opening of the barrel to a distance from the front end opening into a sealing engagement with the barrel interior to form a chamber between the piston and front end opening. In charging step 44 the solution to be lyophilized is filled into the front chamber and the solution is lyophilized in step 45. Next 46 the barrel front end is sealed in-situ in the lyophilizing chamber. A solvent for the lyophilized powder is filled into the rear chamber in step 47. In step 48 a rear piston is inserted into the barrel rear end to confine the solvent in the rear chamber. The preparations in the barrel are now sealed from the surroundings and the prefilled barrel can leave the sterile zone 40. In a final assembly step 49, further components can be added, such as a sealer capping and rear actuating means, preferably by use of a sleeve as intermediate component as described. It is clear that all components charged into the barrel, notably the intermediate piston and the rear piston as well as the solution and the solvent, have to be sluiced into the sterile zone 40 in sterile condition.--

Please replace the paragraph starting on page 25, line 5 with the following paragraph:

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--In the above process it is preferred to use the ampoule carrier of the invention in all steps 43 to 48 performed within the sterile zone 40. Due to the carrier versatility it is also

possible and preferred to use the carrier in the sterilization oven of step 42 and the carrier can be used in the washing and siliconizing step 41 although these steps can also be conducted with the ampoules in bulk or in blisters. It is generally preferred to remove the ampoules from the carrier before conducting the assembly steps 49. It is generally preferred to turn the ampoules with the carrier upside down between steps 46 and 47, and preferably this is the only turning step until ampoule removal from the carrier. In case the ampoules are of the preferred syringe type described all steps up to 46 inclusive can with preference be conducted from the upper side of the carrier. It is also possible to delay mounting of the sleeve until step 49 outside the sterile zone, which limits the number of components entered into that zone. According to the invention it is possible and preferred to charge the sealers into a carrier rest position, allowing vapor escape, which is preferably done between steps 44 and 45. The in-situ sealing of step 46 is preferably done by axially moving the charged sealers from the rest position into sealing engagement with the barrel front opening.--

In the claims:

Please delete claims 1-20, 28, 79 and 97-102 without prejudice.

Please amend claims 21, 23, 26 and 27 as follows:

--21. (Twice Amended) A process for the manufacture of a prefilled syringe type ampoule having a) a barrel with a front end and a rear end defining an axis therebetween, the barrel having substantially constant cross-section between the front end and the rear end, at least the front end ending in an opening, b) a sealer attached to the front end and sealing the front end opening, c) at least one piston movably and sealingly arranged within the barrel and d) a sleeve extending along